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Lavandula angustifolia biological characteristics: An in vitro study

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Abstract

Objective: Lavender is an aromatic shrub belonging to the Lamiaceae family. The flowers and leaves in different forms of extracts are used as herbal medicine. The accumulation of amyloid beta (Aβ) plaques, reduction of acetylcholine due to hyperactivity of acetylcholinesterase, and glutamate neurotoxicity are known to be involved in decreased level of cognitive function. In our previous study, we proved that the aqueous extract of lavender improves learning and memory. This in vitro study was designed to evaluate antiaggregative, antioxidant, and antiacetylcholinesterase activities of the herbal medicine.

Methods: Thin layer chromatography, high-performance liquid chromatography, thioflavin, atomic force microscope (AFM), Elleman, and 2,2-diphenyl-1-picryl hydrazyl techniques were used for qualitative analysis, quantitative analysis, antiaggregative characteristics, anti-acetylcholinestrase activity and antioxidant activity of the lavender extract, respectively.

Results: We found chromatographic peaks of caffeic acid and luteolin-7-glycosid in the lavender extract. Our results indicated that aqueous extract of lavender dose-dependently inhibits the formation of Aβ aggregate. The AFM technique showed that lavender largely diminished the Aβ fibril formation. We also observed a considerable radical scavenging activity of the extract.

Conclusions: Prevention of Aβ plaque formation and antioxidant activity along with nontoxic features of the lavender extract promise possible effectiveness of this plant on improving some neurological disorders including Alzheimer's disease.

KEYWORDS
amyloid beta, antiacetylcholinesterase, antioxidant, caffeic acid, lavender, luteolin

1 | INTRODUCTION

Lavandula angustifolia (lavender), also known as *Lavandula officinalis*, is a strongly aromatic shrub in the *Lamiaceae* family (Oskouie, Yekta, Tavirani, Kashani, & Goshadrou, 2018). Lavender is native to the Mediterranean region and grows as high as 1–2 m with evergreen leaves (Niksic et al., 2016). The flowers and leaves of lavender either in the form of mostly essential oil or different forms of extracts are traditionally used as therapeutics (Gilani et al., 2000; Méndez-Tovar, Herrero, Pérez-Magariño, Pereira, & Asensio, 2015; Umezu et al., 2006). The main constituents of the essential oil of the herbal medicine are the linalool and linalyl acetate (Caputo, Souza, Alloisio, Cornara, & De Feo, 2016). Several studies have shown that lavender displays multiple pharmacological effects, such as sedative, anticonvulsant, analgesic, and local anesthetic roles (Silva et al., 2015; Soheili, Salami, Haghir, Zali, & Rezaei Tavirani, 2014). It also displays tranquilizing role with soothing and relaxing effect on the nervous system (Lopez, Nielsen, Solas, Ramirez, & Jager, 2017). Data showing the effects of the aqueous extract of lavender is limited. In our previous studies, we showed that the aqueous extract of lavender

improves the impaired learning and memory (Kashani, Tavirani, Talaei, & Salami, 2011) and positively affect the deteriorated synaptic transmission in an animal model of Alzheimer's disease (AD) (Soheili, Rezaei Tavirany, & Salami, 2015). It also clears the amyloid beta (Aβ) plaques from the hippocampus of these animals (Soheili, Tavirani, & Salami, 2012). Accordingly, the present study aimed to standardize the extract based on caffeic acid and luteolin-7-glycosid. Caffeic acid is abundantly found in medicinal plants with anti-inflammatory and antioxidative properties, which is beneficial against neurodegenerative diseases (Park et al., 2004; Parlakpinar, Sahna, Acet, Mizrak, & Polat, 2005; Wei et al., 2008). Luteolin, a flavonoid found in various edibles, has antioxidant and anti-inflammatory activity both in vitro and in vivo (Lopez-Lazaro, 2009). It also has preventive and therapeutic value for neurodegenerative diseases including AD and ameliorates the cognitive impairment in various AD animal models (Fu et al., 2014; Zuo, Hemmelgarn, Chuang, & Best, 2015). Luteolin has specific binding sites for AChE and Aβ42, which might result in the inhibition of AChE activity and Aβ disaggregation or prevent plaque formation (Ali et al., 2018).

In the following, we examined the probable effect of aqueous extract of lavender on in vitro polymerization of Aβ monomers, reduction of acetylcholinesterase (AChE) activity, and its anti-oxidant effect. All the above are known as pathological symptoms of AD.

2 | MATERIALS AND METHODS

2.1 | Chemicals

The standards of caffeic acid and luteolin were purchased from Extra Synthesis (Genay, France). Water used in high-performance liquid chromatography (HPLC) and sample preparation was produced with a Super Purity Water System. Methanol, dimethylsulfoxide (DMSO), and other organic solvents (for HPLC or analytical grade) were obtained from Merck (Darmstadt, Germany). Aβ proteins (1–42), thioflavin T, AChE enzyme, acetylthiocholine iodide (ATCI), 5,5′-dithiobis [2-nitrobenzoic acid] (DTNB), and 2,2-diphenyl-1-picryl hydrazyl (DPPH) were purchased from Sigma-Aldrich (MO). All the reagents and drugs used were of analytical grade.

2.2 | Aqueous extract preparation

For extract preparation, 300 g of dried *Lavandula angustifolia* leaves and flowers (with voucher specimens of 1092) were mixed with 1,000 ml boiled water. The mixture was filtered after 4 hr and concentrated by vaporizing on a water bath.

2.3 | Sample preparation

For HPLC analysis, 50 mg of ground sample was extracted with 25 ml water and sonicated for 10 min. Then, it was centrifuged at 4,500 rpm for 5 min. The residual solid was further extracted with 20 ml of water, sonicated for 5 min, and centrifuged at 4,500 rpm for 5 min. The supernatants were transferred to a 50 ml volumetric flask and water up to 50 ml was added. Before HPLC analysis, the sample was centrifuged at 13,000 rpm for 10 min.

2.4 | TLC analysis

To chemically characterize the presence of caffeic acid and luteolin in aqueous extract of lavender, TLC was carried out with chloroform, acetone, and acid formic as the solvent system.

2.5 | Instrumentation of HPLC

An HP 1100 series liquid chromatography system of Shimadzu was used. The column, Kingsorb 5 µl C8 (250 × 4.6 mm), with photodiode array detector was used. In this experiment, methanol–water and acetonitrile–water in combination with acetic acid or phosphoric acid were tested as the mobile phase.

Then, a 75 min of run with flow rate of 0.8 ml/min was performed. The sample injection volume was 100 µl with a detection wavelength of 325–350 nm. Before injection of the lavender extract, working standard solutions of caffeic acid and luteolin with a concentration of 1.25, 2.5, 5, and 10 µg/ml, respectively, were injected into the HPLC. The standard peaks were depicted and the peaks formula at 325 and 350 nm were obtained. Finally, the lavender extract in a concentration of 500 µg/ml was injected and the concentration percent of caffeic acid and luteolin in the extract were calculated. All experiments were carried out in triplicate.

2.6 | Thioflavin T measurement

The Aβ monomers were dissolved in DMSO (Aβ-DMSO) and kept under −20°C until use. The experiments were performed on Aβ-DMSO in two different conditions. In the control group (CON), the Aβ-DMSO was added to Tris buffer (pH 7.4) and the mixture was incubated at 37°C for 24 hr. In another group, (Treat) Aβ-DMSO was added to Tris buffer + extract and maintained under the same condition. The Treat group itself was subdivided to four groups receiving 1, 5, 10, and 100 µg/ml of the extract and were named as Treat-1, Treat-5, Treat-10, and Treat-100, respectively. After incubation, 1 mg thioflavin T was dissolved in 1 ml deionized water and added to the mixtures. Then, using a microplate reader (Spectramax Gemini XS; Molecular Devices, Sunnyvale, CA) with a special filter set (excitation at 442 nm and emission at 485 nm), the fluorescence of the thioflavin T bound to Aβ aggregates was measured. Finally, optical density (OD) of the control group was compared with that of the four treated groups.

2.7 | AFM imaging

The samples were imaged using a Veeco atomic force microscope (AFM) with the noncontact imaging mode. AFM consists of a sharp tip (probe) at its end. When the tip is brought into proximity of a sample surface, mechanical contact of the tip and the sample lead to

image formation. The method was carried on as previously described (Soheili, Khalaji, Mirhashemi, & Salami, 2019). In brief, the samples were prepared, for AFM imaging, by drying a 5 μL sample from the Treat-100 group on freshly cleaved mica plates. Mica plates containing the samples were dried for about 2 min at ambient temperature. After that, the buffer and salt components were washed from the surface of mica with deionized water and the mica was dried again. This procedure ensures that the fibrils and peptide molecules remain attached to the mica surface, possibly due to the negative charge on the surface of mica plates.

2.8 | Cell lines

Human hepatoma G2 (HepG2) cell line was obtained from Pasture Institute of Iran (Tehran, Iran). The cell line (100,000 cells/well) was cultured in a suitable medium for desired growth, along with 5% or 10% fetal bovine serum in a humidified incubator at 37°C in an atmosphere of 5% CO_2. The cells were treated with different concentrations of the aqueous extract of lavender (6.25, 12.5, 25, 50, and 100 μg/ml) for 24 hr for the determination of lavender cytotoxicity.

2.9 | AChE inhibitory assay

Ellman assay is usually applied to define the cholinesterase activity of materials. In 96-well plates, 125 μl of 3 mM DTNB, 25 μl of 15 mM ATCI, and 50 μl of phosphate buffer (pH 8) and 25 μl of the samples (extract or methanol) were dissolved in methanol (3 mg/ml) and added to the wells. A concentration range of lavender extract (100, 150, 200, 250, and 300 μg/ml) was used in the AChE assay experiments. The absorbance was measured at 405 nm every 13 s for 65 s; 25 μl of 0.22 U/ml of AChE enzyme was then added and the absorbance was again read every 13 s for 104 s. The absorbance was plotted against time and the enzyme activity was calculated from the slope of the line. Any increase in the absorbance due to the nonenzymatic hydrolysis of the substrate was corrected by subtracting the rate of reaction before addition of the enzyme from the rate after addition of the enzyme. Percentage of enzyme inhibition was calculated by comparing the rates of the samples with the blank.

2.10 | 2,2-Diphenyl-1-picryl hydrazyl (DPPH) radical scavenging assay

This method is one of the most extensively used antioxidant assays for plant samples. To determine DPPH radical scavenging activity of lavender samples, 2 ml of 100 μM DPPH methanol solution was added to 2 ml of the various concentrations of the extract. The mixture was shaken vigorously and left at room temperature for 30 min. Then, the absorbance of the solution was read at 517 nm and the antioxidant activity was calculated using the following equation:

Percent of scavenging capacity = 100 − [(ABS of sample − ABS of blank) × 100/ABS of control].

A mixture of 2 ml methanol with 2 ml plant extract solution was used as the blank, whereas 2 ml DPPH solution plus 2 ml solvent corresponding to the extract was used as the negative control. Vitamin C was used as a positive control with concentrations of 1, 1.5, 2, 2.5, 3 μg/ml, respectively. The extract concentration providing 50% inhibition (IC_{50}) was calculated from the plot of inhibition percentage against extract concentration. All tests were performed in triplicates.

2.11 | Data analysis

Statistical analysis was performed using one-way analysis of variance followed by LSD post hoc test. The differences were considered significant for $p < 0.05$. The data are expressed as mean ± *SEM*.

3 | RESULTS

3.1 | Standardization of aqueous extract of lavender

In this experiment, methanol–water and acetonitrile–water in combination with acetic acid or phosphoric acid were tested as mobile phase. Meanwhile, it is necessary to clarify whether a gradient or isocratic system has been used. The best separation of caffeic acid and luteolin-7-glycosid was found in methanol–water system containing phosphoric acid (Figure 1).

Comparing the lavender and standard chromatograms, the chromatographic peaks of caffeic acid and luteolin-7-glycosid were confirmed. Figure 2a,b show the spectra of caffeic acid and luteolin-7-glycosid. The best separation was achieved within 21 min for caffeic acid and 53 min for luteolin-7-glycosid at 325 nm (Table 1). The amount of caffeic acid and luteolin-7-glycosid in 100 μl of the aqueous extract of lavender were estimated at 13 and 41 μg/ml, respectively.

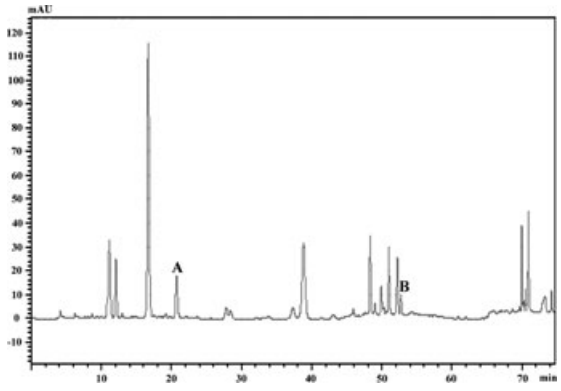

FIGURE 1 HPLC profile of aqueous extract of lavender. (a) and (b) represents caffeic acid and luteolin peaks, respectively. HPLC: high-performance liquid chromatography

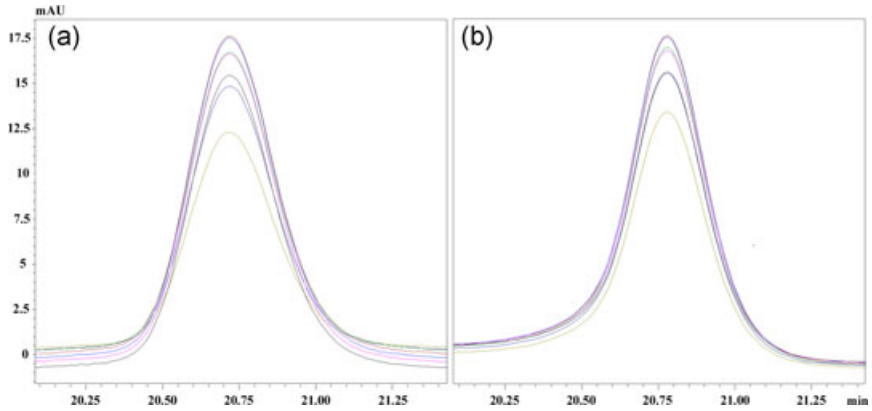

FIGURE 2 The standard chromatogram sample of caffeic acid (a) and luteolin (b) [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 The concentration percent of caffeic acid and luteolin in 1 ml of aqueous extract of lavender in the wavelengths of 325 and 350 nm, respectively

Wave length (nm)	Name of component	Concentration (%)
325	Caffeic acid	0.1
350	Caffeic acid	0.1
325	Luteolin	0.528
350	Luteolin	0.47

3.2 | Antiaggregative effect

With respect to the clearance effect of lavender on Aβ fibrils from the hippocampus of the Aβ-treated rats (Soheili et al., 2012), concentration dependencies were examined by using the thioflavin T method (Figure 3). We observed that the extract induced a concentration-dependent decline in fluorescence intensity in Aβ 1–42 ($F_{4,\ 16} = 4.803$; $p = 0.01$). Our results showed that the dose of 1 μg/ml had no significant effect on Aβ aggregation ($p = 0.273$). The doses of 5, 10, and 100 μg/ml, respectively, had a considerable effect on Aβ polymerization and aggregate formation ($p = 0.025$, 0.008, and 0.001, respectively). These findings prove that the aqueous extract of lavender dose-dependently inhibits the formation of Aβ aggregate.

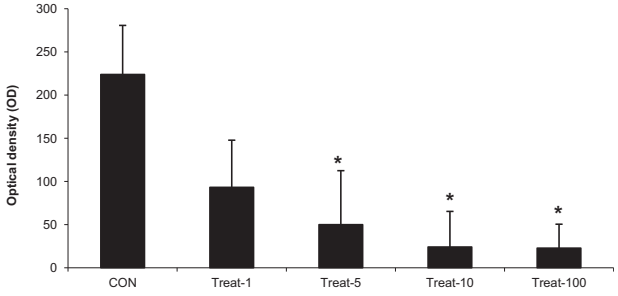

FIGURE 3 Dose-dependent effect of aqueous extract of lavender on Aβ polymerization. The doses of 5, 10, and 100 μg/ml significantly inhibited the polymerization of Aβ (*$P < 0.05$, compared to CON). Aβ: amyloid beta

3.3 | AFM imaging

To visualize the effect of the herbal extract on Aβ fibril formation, the fibrils were observed by AFM technique. A clear and shining paired helical Aβ was visible in the Aβ treated without the extract, which is reflected in thicker and longer aggregated fibrils (Figure 4a,b). In contrast, the incubation of Aβ with the aqueous extract of lavender largely diminished the fibril formation (Figure 5a,b). The fibril characteristics of the Aβ peptide treated with and without extract are summarized in Table 2. Figures 4,5c illustrate height profiles of the fibrils with and without extract, respectively.

3.4 | Cytotoxic activity

We also evaluated the cytotoxicity effect of aqueous extract of lavender on the HepG2 cell line. The microscopic evaluation of the HepG2 cells indicated no granulation and no adherence to the flask of the treated cells when compared with the control. The cell count using a Neubauer chamber did not reveal any difference between the two groups. These data confirmed that the aqueous extract of lavender had no toxic effect on the HepG2 cell line (Figure 6).

3.5 | AChE inhibitory activity

The results of AChE inhibitory activity of aqueous extracts of lavender at the concentration of 300 μg/ml are illustrated in Figure 7. The plant extracts showed no enzyme inhibition activity ($F_{3,\ 11} = 0.368$; $p = 0.21$).

3.6 | Antioxidant activity

Our findings demonstrated that the lavender's aerial parts display a considerable radical scavenging activity dose-dependently ($F_{3,8} = 763.712$; $p < 0.0001$). Figure 8 illustrates the severity of antioxidant activity of different doses of the extract.

However, the extract showed a lower antioxidant activity in comparison with vitamin C, which was used as standard (Figure 9).

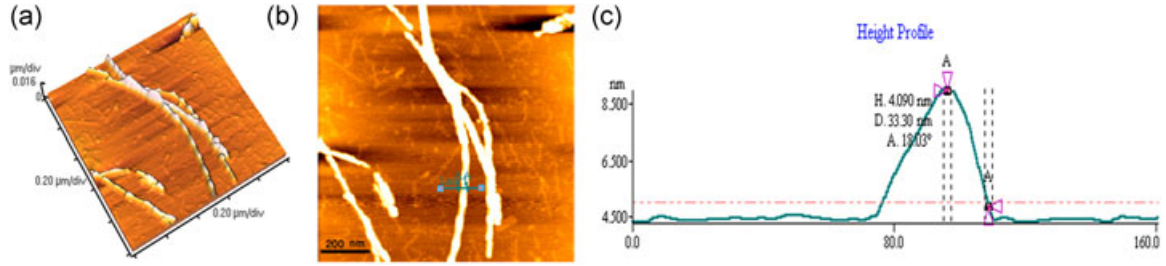

FIGURE 4 The AFM imaging of 3D (a) and 2D form (b), and height profile (c) of Aβ peptide treated without the aqueous extract of lavender. A clear and shining fibril of Aβ is visible. A: angle with horizon (degree); Aβ: amyloid beta; D: distance between the two A points (nm); H: height (nm) [Color figure can be viewed at wileyonlinelibrary.com]

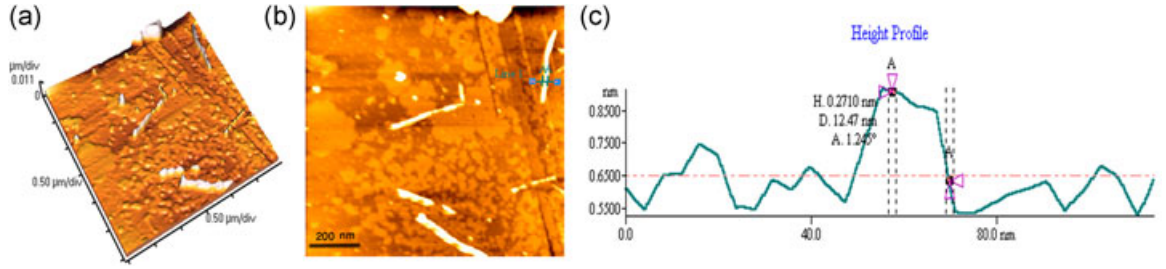

FIGURE 5 The AFM imaging of 3D (a) and 2D form (b), and height profile (c) of Aβ peptide treated with the aqueous extract of lavender. The extract of lavender inhibited fibril formation of Aβ. A: angle with horizon (degree); AFM: atomic force microscopy; Aβ: amyloid beta; D: distance between the two A points (nm); H: height (nm) [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

Lavandula angustifolia is an aromatic herbal medicine having multiple effects. Antioxidative and anti-inflammatory characteristics are attributed to lavender (Marín, Sayas-Barberá, Viuda-Martos, Navarro, & Sendra, 2016; Silva et al., 2015) which, in turn, show similarities to the neuroprotective and neurotrophic properties of the herbal medicine (Parejo et al., 2002).

The HPLC results verified that the two constituents of the lavender aqueous extract are the caffeic acid and luteolin. Caffeic acid is a natural phenolic compound, which has the potential to minimize oxidative stress and inflammatory responses and may potentially be of value in the treatment of neurodegenerative diseases (Bailly & Cotelle, 2005; Pittalà et al., 2015; Yang et al., 2013). Luteolin, as a flavonoid compound of food, protects hippocampus against the damage induced by kainic acid in rats (Lin, Lu, & Wang, 2016). Luteolin also has some other biological functions, such as relieving neuroinflammation through reduction of proinflammatory mediators and antioxidant activity (Jang, Dilger, & Johnson, 2010; Wang, Wang, Cheng, & Che, 2016). Taken together, it is suggested that luteolin could potentially be used against neurodegenerative diseases, including AD. Luteolin is also known to have memory-improving effects (Jang, Dilger, & Johnson, 2010).

The accumulation of Aβ is recognized as one of the main cause of Alzheimer's disease (Gunther & Strittmatter, 2010). The Aβ plaques affect the function of *N*-methyl-D-aspartic acid (NMDA) receptors (Sinnen, Bowen, Gibson, & Kennedy, 2016). In contrast, the NMDA ion channel receptors mediate the main excitatory neurotransmission in the brain and the excessive activity of the receptors is known to be involved in the Alzheimer's disease (Dal Prà, Chiarini, & Armato, 2015). It is demonstrated that the administration of lavender extract can alleviate the extracellular accumulation of the NMDA receptor and reduce the glutamate neurotoxicity (López, Nielsen, Solas, Ramírez, & Jäger, 2017). Accordingly, the prevention of Aβ plaque formation, as reported here, promises probable positive effect of the

TABLE 2 The fibril characteristics of Aβ peptide treated with and without the extract

Aβ	*H* (nm)	*D* (nm)	*A* (degree)
Without the extract	4.090	33.30	18.3
With the extract	0.271	12.47	1.245

Note. A: angle with horizon; Aβ: amyloid beta; D: distance between the two A points; H: height.

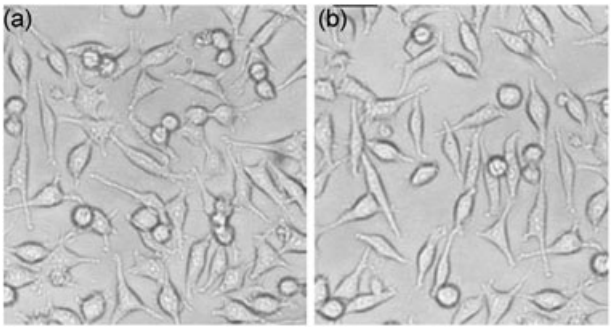

FIGURE 6 The aqueous extract of lavender (100 μg/ml) had no toxic effect on the HepG2 cell line. The control (a) and treated cell lines (b) display the same morphology

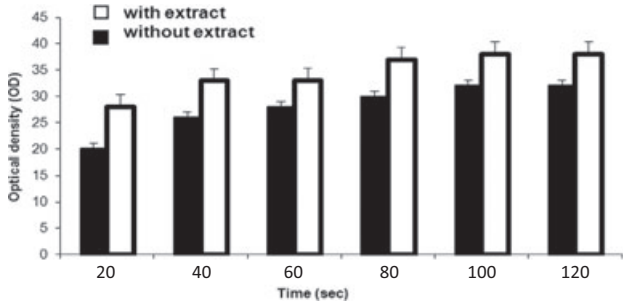

FIGURE 7 The effect of aqueous extract of lavender on AChE activity at the concentration of 300 μg/ml. No considerable impact was found even after 120 s of the extract treatment.
AChE: acetylcholinesterase

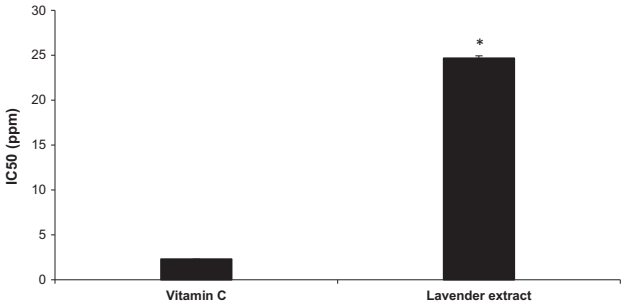

FIGURE 9 Comparing the antioxidant activity of aqueous extract of lavender with vitamin C. The extract showed lower antioxidant activity in comparison with vitamin C (*$p < 0.0001$)

aqueous extract of lavender on the neurological disorder, such as the Alzheimer's disease (Soheili et al., 2012; Thal, 2015).

The findings of this study indicated that the herbal medicine displayed no inhibitory effect on the activity of AChE. AChE is found at the cholinergic synapses, where its activity serves to terminate synaptic transmission. The cholinergic neurotransmission takes a role in learning and memory phenomena (Lian et al., 2017). On the basis of the present results, possible improving role of the lavender on spatial memory cannot be attributed to its inhibitory effect on the activity of AChE. A possible mechanism can be cross-talk between the herbal extract and the NMDA receptors, known as the important receptors in neuronal hippocampal circuits involved in the spatial learning and memory. However, such assumptions need to be further investigated.

A potent antioxidant activity was observed under the in vitro assessment. Many studies suggested that oxidative stresses promote the production and deposition of Aβ (Zuo et al., 2015). Oxidative stress is an imbalance between the production of free radicals in the body and its ability to quench it through antioxidants (Chang et al., 2014). There is also evidence that though Aβ deposits lead to more mitochondrial damage; mitochondria-targeted antioxidants prevent abnormal Aβ processing and decrease plaque formation (Han et al., 2017). Consequently, it can be said that the herbal extract might have a supporting role in combating the antioxidant activity.

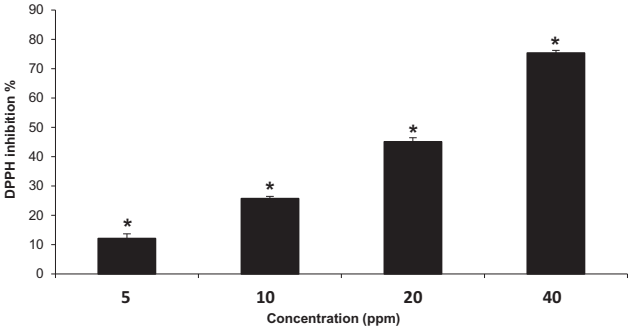

FIGURE 8 DPPH method was applied to assess the radical scavenging activity of the aqueous extract of *Lavandula angustifolia*. The antioxidant activity of the extract was observable in all concentrations (*$p < 0.05$ compared to the CON group; the value, not shown, is = 0).

Taken together, the aqueous extract of lavender opposes Aβ fibrillation and, hence, prevents plaque formation. Further, our results proved that the herbal medicine displayed antioxidant activity. Moreover, in the concentrations used in this study, the lavender extract had no toxic effect. Therefore, due to its biological properties, the extract could be effective in inhibiting inflammatory and oxidative effects. Accordingly, some neurological disorders, including Alzheimer's disease could possibly be treated by the lavender aqueous extract.

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CONFLICTS OF INTERESTS

The authors declare that there are no conflicts of interest.

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